The effects of diabetic metabolic derangement on left ventricular structure and function

I. Heinonen,[1,6] O. Sorop,[1] M. van Kranenburg,[1,2] V.J. de Beer,[1] Y. Octavia,[1] R.W.B. van Duin,[1] R.J. van Geuns,[1] A.H. van den Meiracker,[3] A.H. Danser,[3] J. van der Velden,[4,5] D. Merkus[1] and D.J. Duncker,[1] [1]Department of Cardiology, Erasmus University Medical Center, 3015CE Rotterdam, The Netherlands, [2]Department of Radiology, Erasmus University Medical Center, 3015CE Rotterdam, The Netherlands, [3]Department of Internal Medicine, Erasmus University Medical Center, 3015CE Rotterdam, The Netherlands, [4]Department of Physiology, VU University Medical Center, 1081 HV Amsterdam, The Netherlands, [5]ICIN-Netherlands Heart Institute, 3508 GA Utrecht, The Netherlands and [6]Turku PET Centre, University of Turku and Turku University Hospital, 20521 Turku, Finland. (Introduced by Stephen Rattigan)

Diabetes is a metabolic condition with continuously increasing incidence, contributing to higher cardiovascular mortality, but its pathophysiological features particularly at the cardiac cellular level are still incompletely understood. In the present study, the effects of diabetic metabolic derangement (DMD, induced by streptozotocin followed by high fat and high cholesterol diet for 6 months) on left ventricular (LV) structure and function were investigated in a large Yorkshire swine animal model highly resembling the human heart. DMD resulted in marked hyperglycemia, hypercholesterolemia, and hypertriglyceridemia as well as systemic inflammation, associated with impaired small coronary artery vasodilation to bradykinin indicative of endothelium-dependent coronary artery dysfunction. Robustly increased superoxide production in the LV was also documented in the DMD, associated with increased eNOS uncoupling and reduced myocardial NO production. These abnormalities were associated with increased myocardial collagen content and elevated passive stiffness of the single cardiomyocyte as assessed *in vitro.* DMD resulted also in smaller heart size and smaller end-diastolic volume, but global LV function was not yet significantly affected as E/A ratio, ejection fraction and end-diastolic stiffness were not different from the control levels. In conclusion, diabetic metabolic derangement induces numerous alterations at the left ventricular tissue level, which are likely to contribute to increased cardiovascular morbidity and mortality in diabetes. Importantly, as these alterations precede impairments in cardiac function, it is also likely that these cellular alterations are potential underlying causes of diabetic cardiomyopathy which then later lead to decrements in global LV function as DMD progresses.